UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 27 1989 007371

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sumithrin (d-phenothrin) - Review of Rat Reproduction Study

Caswell No.: 652B

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The rat reproduction study is acceptable as Core-Guideline. The NOEL is 1000 ppm, the mid-dose.

At 3000 ppm (HDT), there was decreased body weight (4 to 6%) in F_0 females, increase in absolute and relative liver weight in F_0 females, slight decrease in litter size at day 1 for F_1B litters, decrease in mean body weight (6%) of F_1 adult males, decrease in body weight of F_2B offspring at day 25, decreased absolute heart and kidney weight of F_2B male offspring, an increase in relative liver weight of F_2B male and female offspring, and an increase in absolute and relative spleen weight, decrease in absolute uterine weight, and increase in relative liver weight in F_1 female adults.

Reviewed By: William Dykstra William Dykstra 7/21/89
Section I, Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Edwin Budd
Section I, Toxicology Branch I - IRS (H7509C) 7/21/89

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DATA EVALUATION REPORT

Study Type: 83-4; Reproduction - Rat

TOX Chem No.: 652B

Accession No.: N/A

MRID No.: 402764-04
Vol. 1-4

Test Material: d-phenothrin, S2539-F

Synonyms: Sumithrin

Study Numbers: 85/SUM009/331; ET-61-0101

Sponsor: Sumitomo

Testing Facility: Life Science Research, England

Title of Report: Sumithrin: Effects Upon Reproductive Performance of Rats Treated Continuously Throughout Two Successive Generations.

Author: J.M. Tesh, et al.

Report Issued: November 1986

Conclusions:

The NOEL is 1000 ppm (mid-dose). The LEL is 3000 ppm (HDT).

At 3000 ppm (HDT), the effects are decreased body weight (4 to 6%) of F_0 females, increase in absolute and relative liver weight in F_0 females, slight decrease in litter size at day 1 for F_1B litters, decrease in mean body weight (6%) of F_1 adult males, decrease in body weight of F_2B offspring at day 25, decreased absolute heart and kidney weight of F_2B male offspring, an increase in relative liver weight of F_2B male and female offspring, and an increase in absolute and relative spleen weight, decrease in absolute uterine weight, and increase in relative liver weight in F_1 female adults.

Classification: Core-Guideline

Special Review Criteria (40 CFR 154.7): N/A

Review:

- Sumithrin: Effects Upon Reproductive Performance of Rats Treated Continuously Throughout Two Successive Generations (Life Science Research, England; Lab Project ID 85/SUM009/331; Sumitomo #ET-61-0101; November 1986).

A. Materials:

1. Test Material - A 20 kg sample of Sumithrin (Lot No. 21005) was used during the study; Name: d-phenothrin, S2539-F; Purity: 92.9%; Chemical class: synthetic pyrethroid; Appearance: clear yellow viscous liquid; Storage conditions: 4 °C.

2. Test Animals - Species: Rat; Strain: Sprague-Dawley; Age: 24 days; Weight: Males 155 to 243 g, females 130 to 186 g; Source: Charles River, U.K.

B. Study Design:

1. Randomized groups of 30 male and 30 female Sprague-Dawley rats (the F_0 generation) were administered 0, 300, 1000, and 3000 ppm of test material in the diet. Food and water were available ad libitum.

   After 13 weeks on the test diets, the F_0 male and female rats were mated to produce the F_1a litters. Following weaning up to day 25 and after a 10-day rest period on the diet, the F_0 parents were mated again to produce the F_1b litters.

   Following weaning, randomized groups of 30 male and 30 female offspring of the F_1b litters were selected to form the F_1 parents.

   The randomized groups of 30 male and 30 female F_1 parents (F_1 generation) were fed their respective diets for 13 weeks. The F_1 parents were then mated to produce the F_2A litters.

   Following weaning and a 10-day rest period on diet the F_1 parental rats were again mated to produce the F_2B offspring.

   Randomized groups of F_2B offspring were fed their respective diets for 13 weeks (F_2 generation).

   All animals were observed daily for toxic signs. Any animals found dead or killed in extremis were given a thorough gross necropsy.

2. Diet Preparation - Diet was prepared once every 2 weeks and stored at room temperature. Samples of treated food were analyzed for stability and concentration at each preparation.

Results

a. F_0 Generation - Dietary analysis of the F_0 diets during the study showed that the achieved concentrations of test material in the diet were acceptable. They ranged from 268 to 336 ppm for the low dose, 924 to 1120 ppm for the mid dose, and 2690 to 3210 ppm for the high dose.

b. F_1 Generation - Dietary analysis of the concentration of test material in the diet showed ranges of 101 to 108 percent for the 300 ppm group, 95 to 111 percent for the 1000 ppm group, and 93 to 101 percent for the 3000 ppm group in comparison to intended concentrations.

c. F_2 Generation - Dietary analysis of the F_2 prepared rodent diet showed low-dose levels ranging from 101 to 108 percent, mid-dose levels ranging from 95 to 111 percent, and high-dose levels ranging from 91 to 101 percent of the intended concentrations.

3. Animals received food (Spratt's Laboratory Diet No. 2, ground, now marketed as Scientific Feeds Laboratory Animal Diet No. 2) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: Student's t-test and Dunnett's t-test were used for body weight and organ weight; Mann-Whitney U-test was used for precoital interval and gestation length; Chi-Square and Fischer's Exact Test were used for mating and reproductive indices and sex ratio.

C. Methods and Results:

1. Observations - Animals were inspected daily for signs of toxicity and mortality.

Results

F_0 Generation - There were no compound-related effects in toxic signs during the F_0 generation. During week 21 of the study, about 60 percent of all males (both control and treated) showed signs typical of infection by an SDA-type virus. The infection did not affect the study.

F_1 Generation - There were no compound-related toxic signs.

F_2 Generation - There were no compound-related toxic signs.

Mortality

F_0 Generation - There were no compound-related effects on mortality.

F_1 Generation - There were no compound-related effects. Two control females and one high-dose female died, but necropsy did not reveal any compound-related effects.

F_2 Generation - There were no compound-related effects. One control male and one control female died during the 13-week feeding period.

2. Body Weight - Body weight was measured weekly for the F_0, F_1, and F_2 parental rats.

Results

F_0 Parents - Analysis of group mean body weight of the F_0 males during the growth phase showed no compound-related effects.

Analysis of group mean body weight of the F_0 females during the growth phase, before pairing, showed a statistically significant decrease (4 to 6%) in the high-dose group in comparison to controls. This high-dose decrease in body weight in parental females is considered compound-related (see Figure 3, attached, from the report).

F_1 Parents - Mean body weight of high-dose males during the growth phase was about 6 percent less than control, but this decrease was not statistically significant. However, this decrease is considered compound-related (see Figure 19, attached, from the report).

Mean body weight of treated females was comparable to controls.

F_2 Parents - There were no compound-related effects in body weight.

3. Food Consumption, Food Efficiency, and Water Intake - Food consumption was determined weekly, water consumption daily, and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the food consumption and body weight gain.

Results

F_0 Generation - There were no compound-related effects in food consumption or food efficiency in F_0 males and females during the growth phase.

There were no compound-related effects in water intake during the F_0 growth phase in males and females.

F_1 Generation - Food consumption and food conversion efficiency was comparable between control and treated groups for both sexes.

Water intake was comparable for male and female treated groups in comparison to controls.

F_2 Generation - There were no compound-related effects in food consumption, food conversion efficiency, and water intake in male and female rats.

4. Evaluation of Mating and Reproductive Indices - Analysis of the mating and reproductive performance consisted of determining the following indices:

Mating Index = [Females mated]/[Females placed for mating] x 100

Fertility Index = [Pregnant females]/[Females placed for mating] x 100

Conception Rate = [Pregnant females]/[Females mated] x 100

Maternal performance was determined as:

Gestation Index = [Rats with live pups]/[Pregnant rats] x 100

Litter data were assessed by the following indices:

Viability Index = [Live pups on day 4*]/[Live pups on day 0] x 100

Survival Index = [Live pups on day 7* or 14*]/[Live pups on day 4*] x 100

Lactation Index = [Live pups on day 21*]/[Live pups on day 7*] x 100

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*Postpartum day.

Additionally, pup body weight, sex ratio, physical and visual function were also investigated.

Results

F_0 Generation - There were no compound-related effects in F_0 female estrus cycles.

There were no compound-related effects in precoital interval, mating, conception rate, and fertility index in the F_0 generation during the F_1A or F_1B litters.

The fertility index for males of the F_1A litters was 83, 90, 83, and 93 percent for the control, low-, mid-, and high-dose groups, respectively.

The fertility index for females of the F_1A litters was 90, 90, 83, and 93 percent for the control, low-, mid-, and high-dose groups, respectively.

The fertility index for males of the F_1B litters was 90, 97, 90, and 90 percent for the control, low-, mid-, and high-dose groups, respectively.

The fertility index for females of the F_1B litters was 90, 97, 90, and 90 percent for the control, low-, mid-, and high-dose groups, respectively.

There were no compound-related effects in gestation length or gestation index in female rats during the F_1A and F_1B litters.

The majority of females in all groups littered after a gestation period of 22 to 23 1/2 days and there was no evidence of dystocia.

For the F_1A litters, the gestation index was 100, 100, 100, and 96 percent for control, low-, mid-, and high-dose females, respectively.

For the F_1B litters, the gestation index was 96, 96, 100, and 100 percent for control, low-, mid-, and high-dose females, respectively.

There were no compound-related effects in appearance or general behavior of F_1A and F_1B offspring up to weaning.

With respect to litter sizes at day 1, there were no compound-related effects in the F_1A litters.

For the F_1B litter, there was a slight decrease in litter size at day 1 in the high-dose group.

The day 1 mean litter sizes for the F_1A litters were 12.5, 12.3, 13.3, and 12.2 pups for the control, low-, mid-, and high-dose groups, respectively.

The day 1 mean litter sizes for the F_1B litters were 13.0, 13.6, 12.7, and 11.9 pups for the control, low-, mid-, and high-dose groups, respectively. The slight decrease in the litter size of high-dose pups in the F_1B litters may be compound-related.

There were no compound-related effects in live birth index, viability index, or lactation index for the F_1A and F_1B litters. All indices were between 94 to 100 percent and there were no dose-related trends in either litter.

There were no compound-related effects in pup mean body weight at postpartum days 1, 4, 10, 14, 21, and 25 for the F_1A and F_1B litters. Additionally, sex ratio of the F_1A and F_1B litters showed no compound-related effects.

With respect to the F_1B litters, there were no compound-related effect in the rate of physical development, as indicated by pinna unfolding, hair growth, tooth eruption, eye opening, or auditory and visual function.

Results

F_1 Generation - Estrus cycles of the treated females were comparable to controls.

For the F_2A and F_2B litters, adult male and female fertility indices were comparable between control and treated groups.

For the F_2A mating, the fertility index in males was 63, 67, 63, and 77 percent for the control, low-, mid-, and high-dose groups, respectively. The fertility index in females was 77, 77, 77, and 90 percent for control, low-, mid-, and high-dose groups, respectively.

For the F_2B mating in males, the fertility index was 69, 66, 77, and 79 percent for control, low-, mid-, and high-dose groups, respectively. For the F_2B mating, the fertility index for females was 72, 66, 80, and 83 percent for control, low-, mid-, and high-dose groups, respectively.

The length of gestation was 22 to 23 1/2 days for females of the F_2A and F_2B litters and there were no compound-related effects in gestation length.

There were no compound-related effects in litter size for the F_2A and F_2B litters.

There were no compound-related effects in live birth index, viability index, and lactation index for F_2A and F_2B litters.

For all groups of the F_2A litters, live birth indices ranged from 96 to 98 percent, viability index at day 4 ranged from 87 to 97 percent, and lactation indices ranged from 92 to 99 percent.

For all groups of the F_2B litters, live birth indices ranged from 99 to 100 percent, viability index at day 4 ranged from 87 to 94 percent, and lactation indices ranged from 90 to 100 percent.

Group mean body weights of the F_2A pups were comparable between control and treated groups during lactation.

For F_2B pups, the mean body weight of the high-dose group was slightly decreased in comparison to controls on day 25 (control, 71.1 g; high dose, 66.0 g). The decreased body weight was not statistically significant but may be compound-related, nevertheless.

Sex ratio was unaffected by treatment for F_2A and F_2B litters.

For the F_2B litters, there were no compound-related effects in pinna unfolding, hair growth, tooth eruption, eye opening, or auditory and visual responses.

5. Sacrifice and Pathology - All animals that were sacrificed on schedule were subject to gross pathological examination. The following checked (X) tissues from parental animals and pups were examined histologically. The (XX) organs in addition were weighed.

X	Digestive system
	Tongue
	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
	Cecum*
	Colon*
X	Rectum*
XX	Liver*
	Gallbladder*
X	Pancreas*
	Respiratory
X	Trachea*
XX	Lung*

X	Cardiovasc./Hemat.
	Aorta*
XX	Heart*
X	Bone marrow*
X	Lymph nodes
XX	Spleen*
X	Thymus*
	Urogenital
XX	Kidneys*
X	Urinary bladder*
XX	Testes*
XX	Epididymides
XX	Prostate
XX	Seminal vesicle
XX	Ovaries
XX	Uterus*

X	Neurologic
XX	Brain*
	Periph. nerve*
	Spinal cord (3 levels)
XX	Pituitary*
X	Eyes (optic n.)*
	Glandular
XX	Adrenals*
	Lacrimal gland
	Mammary gland
	Parathyroids*
XX	Thyroids*
	Other
	Bone*
	Skeletal muscle*
	Skin
X	All gross lesions and masses

*Recommended by Subdivision F (October 1982) guidelines for chronic studies.

Results

F_0 Generation - Necropsy of F_0 parental animals did not reveal any compound-related findings.

Analysis of absolute and relative organ weights of F_0 parental animals showed a statistically significant increase in the relative kidney weight of high-dose and mid-dose male rats and an increase in absolute and relative liver weight of high-dose female rats. However, there were no histopathological findings in these organs.

The increase in absolute and relative liver weight in high-dose F_0 females is considered compound-related, since increased relative liver weight was also seen in F_1 females and F_2B male and female weanlings. Individual data for the F_0 females showed that only one control female had an absolute liver weight exceeding 15 g, whereas 12 high-dose females had absolute liver weights exceeding 15 g.

Histopathological evaluation of 20 control and 20 high dose male and female F_0 parental rats did reveal two unusual findings in females, but none in males.

A statistically significant increase in the high-dose in comparison to controls of cystic thyroglossal duct remnants in the thyroid and yellow pigment in suspensory

ligament of the uterus was observed in females. The following table shows the incidence of these findings:

	F_0 Female Rats			
Group (ppm)	0	300	1000	3000
No. Examined	20	0	0	20
Thyroid				
Cystic thyroglossal duct remnants	4	0	0	12*
Uterus				
Yellow pigment in suspensory ligament	10	0	0	19**

*p < 0.05
**p < 0.01

In contrast, histological evaluation of the thyroid and uterus of F_1 adult female rats did not confirm these findings. An incidence of 11/19 in the controls compared to 13/20 in the high-dose for cystic thyroglossal duct remnants in the thyroid and an incidence of 12/19 in the controls compared to 8/20 in the high-dose for pigment in suspensory ligament in the uterus was observed in the F_1 females.

In light of the findings in the F_1 adult females, the histological findings in the F_0 females may not be compound-related.

Necropsy of the offspring of the F_1A and F_1B litters did not show any compound-related effects. The most frequent necropsy observation was the absence of milk or food in the stomach and the incidence of this finding was comparable among groups of the F_1A and F_1B litters.

Results

F_1 Generation - There were no compound-related effects in gross necropsy observation in the weanlings of the F_2A and F_2B litters.

Terminal body weight and absolute heart and kidney weight of the male high-dose group were statistically significantly decreased in comparison to controls.

With respect to relative organ weight, high-dose males had a statistically significant increase in relative liver and brain weight in comparison to controls.

In female F_2B offspring, the high-dose group had a statistically significant increase in relative liver weight in comparison to controls.

Histopathological evaluation of F_2B offspring did not show any compound-related effects in high-dose male and female offspring in comparison to controls.

The decreased body weight and decreased absolute heart and kidney weight in high-dose males and the increase in relative liver weight in high-dose male and female offspring are considered compound-related.

Gross necropsy of F_1 adult males and females did not reveal any compound-related macroscopic findings.

Analysis of absolute and relative organ weights of F_1 adult male rats did not show any compound-related effects.

In female F_1 adult rats, there was a statistically significant increase in absolute spleen weight at the high dose and statistically significant decrease in absolute uterus weight at the mid and high dose in comparison to controls.

The mean absolute uterine weights of the control, low-, mid-, and high-dose groups were 0.72, 0.68, 0.60 and 0.60 g, respectively. Relative uterus weight was statistically significantly decreased in mid-dose but not high-dose females.

Relative spleen and liver weights were increased in high-dose females in comparison to controls.

At the high-dose, the decrease in absolute uterine weight and the increase in absolute and relative spleen and relative liver weights in F_1 female rats are considered compound-related.

The reasons for this conclusion are: 1) For the uterus, both the mid and high dose absolute weights were decreased; 2) both the absolute and relative spleen weights were increased; and 3) the increase in relative liver weight was observed in F_0 females and both male and female F_2B weanlings.

The NOEL for the study is the mid-dose group of 1000 ppm.

Histopathological evaluation of control and high-dose male and female F_1 adult rats did not reveal any compound-related effects.

Results

F_2 Generation - There were no compound-related effects in gross necropsy, absolute or relative organ weight, or histopathology in male and female F_2 adult rats.

Attachments

R:56533:Dykstra:C.Disk:KENCO:4/21/89:rw:vo:jh:rw:vo:AS:EK:AS
R:57229:Dykstra:C.Disk:KENCO:7/19/89:AS:vo:de:rw

Sumithrin toxicology review dated 7/27/89

Page _____ is not included in this copy.

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